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EPISODIC MIGRAINE (S NAHAS, SECTION EDITOR)

Drug Safety in Episodic Migraine Management in Adults. Part 2: Preventive Treatments

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Abstract

Purpose of Review The aim of this review is to aid in decision-making when choosing safe and effective options for preventive migraine medications.

Recent Findings In Part 2, we have compiled clinically relevant safety considerations for commonly used migraine prophylactic treatments. Preventive treatment of episodic migraine includes nonspecific and migraine-specific drugs. While medications from several pharmacological classes–such as anticonvulsants, beta-blockers, and antidepressants–have an established efficacy in migraine prevention, they are associated with a number of side effects. The safety of migraine-specific treatments such as anti-CGRP monoclonal antibodies and gepants are also discussed.

Summary This review highlights safety concerns of commonly used migraine prophylactic agents and offers suggestions on how to mitigate those risks.

Keywords Migraine prevention · CGRP · Antidepressants · Beta-blocker · Anticonvulsants · Risk

Introduction

While preventive treatments are commonly associated with the management of chronic migraine (defined as greater than or equal to 15 headache days per month, with 8 of those days fulfilling diagnostic criteria for migraine or responding to migraine-specific medication), the American Headache Society (AHS) has also established guidelines for prophylactic strategies in those with episodic migraine (EM) [1]. Migraine prophylactic treatments are optional for individuals experiencing 2 moderately disabling headache days per month, but should be standard of care for patients who, on a monthly basis, report either at least 3 severely disabling attacks or 4 or more moderately disabling attacks. Prophylactic treatment should also be offered to any person with at least 6 headache days per month–regardless of level of disability–as well as for those experiencing headache from over-reliance on acute treatments, and those with potentially devastating headache types such as hemiplegic migraine [2••, 3, 4].

Medications used as migraine prophylactic therapy can be categorized based on specificity for migraine as well as level of evidence. In this paper, we will be focusing on preventive treatments with established (level A) and probable (level B) efficacy based on the most recent AHS position statement. Since the focus of this paper is EM, we will not be reviewing onabotulinumtoxinA, as it is FDA-approved for the treatment of chronic migraine specifically. Also, with the exception of CGRP antagonists, potential safety concerns of these medications during pregnancy and lactation will not be covered.

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Nonspecific Migraine Treatments

Beta-adrenergic Receptor Blockers

Beta-adrenergic receptor blockers (beta-blockers) are widely used as migraine prophylaxis since their benefit in "vascular headache" was first reported in 1966 [5].

Since then, two beta-blockers, propranolol and timolol, have been FDA-approved for the prophylactic treatment of migraine. As a group, beta-blockers inhibit epinephrine and norepinephrine from binding to beta-adrenergic receptors [6]. They have various selectivity to adrenoreceptors, as well as different pharmacokinetic properties that can influence their side effects and potential for drug interactions [7].

Selective (or cardioselective) beta-blockers preferentially act on beta-1 receptors in cardiac muscles and lead to reductions in heart rate, cardiac workload, and cardiac muscle contractility. Non-cardioselective beta blockers act at beta-1 receptors, as well as beta-2 receptors located in smooth muscle cells in the lungs, pancreas, bladder, uterus, blood vessels, and gastrointestinal system. Non-selective blockade can affect smooth muscle relaxation in bronchioles, blood vessels, and the uterus, as well as alter metabolic processes such as glycogenolysis and insulin release from pancreatic beta cells [8, 9].

Beta-blockers with established efficacy in migraine prophylaxis include propranolol (non-selective), timolol (non-selective), and metoprolol (selective). Nadolol (non-selective) and atenolol (selective) are probably effective, while possibly effective (level C) beta-blockers include nebivolol (selective) and pindolol (non-selective with intrinsic sympathomimetic activity) [2••, 10•]. Other beta-blockers with intrinsic sympathomimetic activity (acebutolol, alprenolol, oxprenolol) and alpha-adrenergic receptor activity (labetalol, carvedilol) are not effective for migraine prophylaxis [11••].

It is believed that beta-blockers act at several central nervous system (CNS) processes, including serotonin synthesis by blocking 5HT-2C and 5HT-2B receptors, neuronal firing within the locus ceruleus and periaqueductal gray via modulating noradrenergic and GABA-mediated processes, and nitric oxide production through inhibition of nitric oxide synthase [12–15]. Lipophilic beta-blockers, such as propranolol, metoprolol, and timolol, can cross the blood–brain barrier to varying degrees, leading to both positive (migraine prophylaxis) and negative CNS effects (depression, fatigue, and disordered sleep) [15–17].

Depression is a commonly cited side effect of beta-blockers, but with conflicting evidence [18]. A recent cross-sectional study of 14,195 patients with hypertension and a mean age of 75 years showed an increased association with depression and use of lipophilic and non-cardioselective beta-blockers [19]. In contrast, a meta-analysis of 15 randomized, controlled trials that included 35,000 study participants showed no statistical association between beta-blockers and depression in those taking the medications for treatment of myocardial infarction, high blood pressure, or cardiac failure, and only small increased risks of fatigue and sexual dysfunction [20]. Fatigue and sedation are more common in early-generation beta-blockers (propranolol and timolol) compared to late-generation beta-blockers (metoprolol, atenolol, and pindolol) and might be in part due to a drop in total energy expenditure by 5–10% as well as decreased exercise tolerance [20–22].

Beta-adrenergic blockers such as propranolol and metoprolol decrease the firing rate of wakefulness-promoting neurons in the locus ceruleus [23]. Blocking beta-1 receptors can also lead to decreased production of melatonin, further contributing to the development of disordered sleep [24]. Lipophilic beta-blockers such as metoprolol are associated with more sleep interruptions and less restful sleep when compared to placebo and hydrophilic beta blockers such as atenolol; however, both lipophilic and water-soluble beta-blockers can induce nightmares [25]. Sleep changes can be seen after just 7 days of twice daily dosing.

Negative CNS effects of beta-blockers may be mitigated by using lower doses and limiting their use in elderly patients, those with hepatic dysfunction, and individuals with long-standing depressive symptoms [16, 26]. Choosing beta-blockers with less lipophilicity, such as atenolol and nadolol, may also decrease development of CNS side effects–although their evidence with regard to migraine prevention are less convincing [2••, 26]. For disordered sleep due to beta blockers, melatonin supplementation could be considered [27].

The use of non-cardioselective beta-blockers is contraindicated in those with reactive airway disease due to concerns of decreasing pulmonary function and inducing bronchospasm [28], with one fatal outcome reported after use of the ophthalmic beta-blocker timolol in a person with asthma [29]. Cardioselective beta-1 receptor blockers, especially in lower doses, are considered a safer alternative for individuals with asthma who may benefit from their use, for example patients with recent MI or congestive heart failure [30, 31].

Raynaud's phenomenon (RP) and cold hands are reported to occur in approximately 7–14.7% of those taking beta-adrenergic blockers [32, 33]. Non-selective beta-blockers are thought to pose the biggest risk of peripheral vasoconstriction; however, a systematic review of 38 studies that included 57,026 individuals found that both cardioselective beta-1 blockers and non-selective beta-2 blockers were both associated with an increased risk when compared to placebo [32]. Beta-blockers with intrinsic sympathomimetic activity, such as pindolol, have less risk of peripheral vasoconstriction but are also less effective in treating migraine [32].

Beta-blockers can cause impaired glucose metabolism, with new-onset diabetes reported with atenolol and metoprolol use [34, 35]. Nonselective beta-blockers impair beta-2-mediated insulin release, further contributing to metabolic syndrome [36]. The cardioselective beta-blocker nebivolol showed a more beneficial metabolic profile, likely due to

unique agonist activity to beta-3 adrenoreceptors that stimulates lipolysis, and can be considered for migraine prevention in patients with metabolic syndrome [36].

Increased plasma concentrations of rizatriptan, zolmitriptan, frovatriptan, and eletriptan are seen with concomitant use of propranolol [37–39]. The clinical relevance of these interactions is not clear, however, as there are no reports of increased blood pressure or adverse events seen with elevated concentrations of these drugs, and only rizatriptan carries a recommendation to limit dosing (to 5 mg) when prescribed to patients also taking propranolol [39–42]. Propranolol can also potentiate the heartrate-lowering effect of lasmiditan, although this effect was relatively small at 6.5 beats per minute, and complete recovery occurred within 3–4 h in volunteers without migraine [43].

Hemiplegic migraine (HM) is defined as migraine that is associated with fully reversible motor weakness or paralysis, as well as reversible disturbances in vision, language, or sensation [1]. Historically, the use of beta blockers in individuals with HM has been avoided based on case reports of negative effects. Earlier case reports in stroke suggested that beta blockers could reduce cerebral perfusion by increasing vascular resistance, but recent case reports have shown beneficial effects of propranolol by lowering sympathetic tone [44–47]. In fact, intravenous beta blockers are used for rapid blood pressure management prior to administering intravenous thrombolytic therapy in acute ischemic stroke management. At this time, there is no clear contraindication to using beta blockers in individuals with HM. It is generally believed that patients with HM have an increased propensity for cortical spreading depolarization (CSD) by the release of glutamate and activation of NMDA receptors, and medications that act via these pathways may be more appropriate in this condition; still, current evidence is based on case reports [48••].

Antiepileptic Drugs (AEDs)

The antiepileptic drugs divalproex sodium, sodium valproate, and topiramate have level A evidence and are FDA-approved for the preventive treatment of migraine. With regard to their role in migraine, both topiramate and valproic acid products (VPA) facilitate GABAergic activity either by acting at GABAA receptors or inhibiting its degradation [46]. Topiramate also inhibits carbonic anhydrase activity, and both VPA and topiramate have been shown to affect CGRP activity in the CNS [49]. The potential side effects of these drugs include neurologic, gastrointestinal, ophthalmic, and endocrine effects.

Neurologic side effects of AEDs are variable. Postural tremor, dizziness, insomnia, and nystagmus are potential side effects of VPA and improve with cessation of the drug in most cases [50]. Long-term use of VPA can lead to parkinsonism even at therapeutic doses [51]. Cognitive side effects are minimal in VPA, but common in topiramate [52]. Cognitive slowing, memory impairment, and word-finding difficulties usually occur within the first 6 weeks of initiating topiramate treatment, but gradual titration and use of extended-release formulations are associated with fewer cognitive side effects [53]. Although anxiety is less frequent and occurs in approximately 5% of individuals taking topiramate, 40–50% of those who develop this side effect discontinue treatment [53]. Both topiramate and VPA have warnings about suicidal ideation.

VPA does not seem to cause any clinically meaningful ocular side effects [54]. Topiramate can lead to acute angle closure glaucoma (AACG) and acute myopia due to fluid accumulation within the suprachoroidal space, causing anterior displacement of the lens-iris diaphragm. Eighty-five percent of individuals with AACG from topiramate have onset within 2 weeks of starting the medication, with bilateral blurred vision as the most common presenting symptom [55, 56]. The reaction is dose dependent, although a large case series found that 50% of individuals with AACG due to topiramate were on doses of 50 mg or less [55]. These adverse reactions are reversible, with AACG resolving within 24–48 hours of treatment (which includes cessation of topiramate and initiation of medications such as topical cycloplegics) and myopic vision returning to baseline within 1–2 weeks of discontinuing topiramate [56].

Dysgeusia, including metallic taste and distorted perceptions of carbonation, is reported in approximately 10% of individuals taking topiramate [57, 58]. While dysgeusia in general can lead to poor diet and diminished appetite, the associated decreased intake of caffeinated sugary beverages can be a beneficial "side effect" in some individuals with migraine. Unlike topiramate, valproate products can be associated with significant weight gain, hyperinsulinemia, and development of insulin resistance [59•, 60].

Common gastrointestinal side effects of VPA include nausea, vomiting, and diarrhea; however, their incidence decreases after the first 6 months of use. Various degrees of hepatotoxicity are seen in 5–10% of patients taking VPA and can be related to enzymatic activity of VPA or idiosyncratic mitochondrial toxicity [61]. Polypharmacy increases risk of hepatotoxicity from VPA, and co-administration with lamotrigine can increase the risk of idiosyncratic hypersensitivity syndrome reactions [62]. VPA is one of the common causes of drug-induced pancreatitis [63]. Screening tests for liver function, serum amylase, and serum lipase abnormalities should be done prior to initiating treatment, and clinical manifestations of hepatic and pancreatic disease should be monitored, especially within the first 6 months of treatment [59•]. VPA is contraindicated in those with significant risk for hepatic disorders or pancreatitis.

Topiramate can lead to renal calculi, hypokalemia, and metabolic acidosis due to carbonic anhydrase inhibition.

Paresthesia, likely related to metabolic acidosis, occurs in approximately 50% of those taking 100 mg per day [64]. Most cases are mild to moderate, and the consumption of potassium-rich foods such as coconut water, bananas, spinach, and raisins can help diminish bothersome tingling. Hydration and lower doses of topiramate can reduce risk of calcium phosphate stones [65•].

Both VPA and topiramate should be prescribed with caution in women of reproductive age and avoided if effective forms of contraception are not in place. Unlike VPA, topiramate can significantly decrease the efficacy of oral contraceptive pills, with doses greater than 200 mg historically implicated. The concomitant use of topiramate with condoms, spermicides, diaphragms, copper intrauterine devices (IUDs), levonorgestrel-releasing IUDs, and depot medroxyprogesterone acetate are preferred over implants, progestin-only contraceptives, and combined hormonal contraceptives (including pill, patch, and ring) due to concerns of contraceptive failure [66•]. In men, VPA can cause infertility and should not be used in men with low sperm count [67].

Antidepressants

Beneficial effects of antidepressants in the prophylaxis of headache were first reported in the early 1960s [68, 69], and a comprehensive review of antidepressants in migraine prevention was recently published [70]. The American Headache Society lists the tricyclic antidepressant (TCA) amitriptyline and the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine as probably effective in the prevention of EM, especially if other classes of medication are contraindicated or if patients have co-existing mood-related conditions. While not listed in the guidelines, nortriptyline is often used as well, given that it is an active metabolite of amitriptyline [2••].

The effects of amitriptyline in migraine are related to its complex mechanism of action. TCAs primarily have serotonergic and noradrenergic effects, but also act as antagonists at postsynaptic alpha cholinergic (alpha1 and alpha2), muscarinic, and histamine H1 and H2 receptors, which can contribute to somnolence, delirium, and other cognitive symptoms. There has been concern that antidepressants, including TCAs, are associated with an increased risk of dementia, but the magnitude and mechanism of this association remains unclear [71, 72].

Unlike TCAs, serotonin and norepinephrine reuptake inhibitors have little effect on cholinergic and histamine receptors. Venlafaxine is of potential dual benefit in patients with comorbid anxiety. Most of the side effects with venlafaxine are similar to other antidepressants but vary in severity.

Anticholinergic effects of TCAs can lead to "blurry vision" by causing dry eyes and lack of accommodation, as well as diplopia, myopia, and angle-closure glaucoma. Topical cholinergic agents are not helpful in such situations and can cause spasms. Hyposalivation and dry mouth are also common, putting the patient at risk for dental disease. This risk can be decreased by choosing TCAs with the least anticholinergic properties (such as nortriptyline instead of amitriptyline), increasing hydration, use of sugarless citrus-flavored candies and moisturizing mouth washes to induce salivation, and practicing good oral hygiene including regular dental follow-ups. Cholinergic drugs such as pilocarpine can be used as well [73].

Potential cardiac risks from antidepressants are due to their effects on blood pressure or cardiac conduction in patients with known ventricular conduction defects or delays. TCAs affect the conduction system below the bundle of His and have electrophysiologic effects on the heart similar to class-I antiarrhythmic drugs. Patients with pre-existing right or left bundle branch blocks are at increased risk of developing a higher degree AV conduction delay even with lower doses of TCAs. TCAs can also cause prolongation of the QT interval in part by delaying the outward movement of K+ ions via slow K current "I Ks." The risk of torsades de pointes can be mitigated by screening for electrolyte abnormalities, using the lowest effective TCA dose, and avoiding use in patients with pre-existing rhythm/conduction disorders or already taking medications that prolong the QT interval. Of note, torsades de pointes secondary to TCAs have only been reported in cases of drug overdose [74].

Older patients, especially those who have cardiovascular disease and ventricular systolic dysfunction, are at higher risk of developing orthostatic hypotension [75]. The mechanism of this effect is likely due to blockade of alpha-1 adrenergic receptors. Nortriptyline has less risk of orthostatic hypotension compared with other TCAs such as imipramine and amitriptyline [76].

Antidepressants can also have indirect cardiac risk by altering the effects of cardiac medications. TCAs can decrease the absorption of sublingual nitroglycerine by anticholinergic effect. They can be pro-arrhythmic with concomitant use of antiarrhythmic drugs, and they can antagonize the blood pressure–lowering effects of antihypertensive medications [77].

Hyponatremia has been reported in association with antidepressants, with selective serotonin reuptake inhibitors (SSRIs) and venlafaxine (SNRI) more prone to cause hyponatremia than TCAs [78]. Risk factors for developing hyponatremia with antidepressants include prior history of hyponatremia, weight < 50 kg, and history of psychosis [79].

Antidepressants decrease gastrointestinal motility causing constipation, with increased risk seen in elderly patients with sedentary lifestyle, irregular eating behavior, and dehydration. Caution should be used with concomitant use of

medications with a similar side effect profile or if there is prior history of constipation. Although rare, cases of cholestatic hepatitis induced by amitriptyline and venlafaxine have been reported. At least 10 cases of venlafaxine-induced cholestatic hepatitis have been presented in the literature [80, 81]. The mechanism of this injury is unclear but is thought to be due to idiosyncratic reaction related to direct hepatic injury.

Weight gain is a well-established side effect of TCAs, with amitriptyline being the most notorious offender [82]. Even short-term use of TCAs has been reported to cause weight gain. Based on one study, the extent of weight gain ranged from 1.3 to 2.9 pounds per month, as noted over a 6-month period [83]. This effect is seen even in low to moderate doses of amitriptyline and nortriptyline. There are various hypotheses for this weight gain effect: increased appetite because of the blockade of H1 receptors, clinical improvement of depression, and increase in fat reserves because of neurotransmitter alteration in the hypothalamic axis. There are no systemic studies on the pathophysiology of these effects, and even the serotonergic receptor effect, which has a role in appetite, is not well studied [84].

Urinary symptoms secondary to TCAs and SNRIs range from urinary hesitancy and decreased caliber of urinary stream to suprapubic pain with complete urinary retention. Once thought to affect only middle-aged men with benign prostate hypertrophy, urinary side effects are equally prevalent in both men and women. Dose reduction or addition of bethanechol chloride can alleviate these unwanted symptoms. Urinary retention requires immediate urological evaluation and treatment.

Sexual dysfunction is more commonly associated with SSRI and TCA antidepressants than SNRIs [85], and can be affected by many factors including, but not limited to, prior experiences, performance anxiety, mood disorder, low self-esteem, stressors, and other medications. Among TCAs, clomipramine has more serotonergic properties and causes problems with desire and orgasm, whereas nortriptyline is predominantly noradrenergic and causes erectile dysfunction [86]. Patients may not freely disclose sexual side effects, so it is important to screen for them on subsequent visits, as they can impact treatment compliance as well as quality of life. Identifying concomitant use of other medications potentially affecting sexual function is also important; these medications include antipsychotics, mood stabilizers, thiazide and potassium sparing diuretics, beta blockers, and H2 receptor blocking gastroprotective agents.

Serotonin syndrome, or rather serotonin toxicity, is a drug-induced condition due to increased levels of serotonin in the synaptic cleft. Clinical symptoms of serotonin toxicity vary and include altered mental status, neuromuscular abnormalities such as tremors and clonus, and autonomic hyperactivity (e.g., hypertension, tachycardia, mydriasis, diaphoresis) [87, 88]. Several medications can cause serotonin toxicity, including TCAs and SNRIs. When used alone, neither nortriptyline nor amitriptyline are able to induce serotonin toxicity, due to low serotonergic properties. However, when combined with other serotonergic agents, toxicity can occur [89]. Risks of serotonin toxicity with concomitant use of triptans with SNRIs such as venlafaxine were previously addressed in Part 1.

Migraine-Specific Treatments

Triptans

Menstrual migraine, which begins 2 days prior and up to 3 days after the onset of menses, can occur solely during menstruation (pure menstrual migraine, PMM) or during menstruation, as well as other times of the month (menstrually related migraine, MRM) [90]. In addition to the acute treatment of migraine, frovatriptan also has level A evidence as a preventive treatment of menstrual migraine. Its long half-life of 26 hours lends itself as an effective "mini-prophylactic" option for women experiencing perimenstrual attacks. Potential safety risks of triptans were discussed in Part 1 of this review series; however, one additional point of concern when using frovatriptan as a mini-preventive treatment in women with MRM is overuse of acute medications, potentially increasing risk for Medication-overuse Headache (MOH). In women experiencing many migraine attacks per month–including a week of MRM–it is best to start a preventive treatment to address the overall condition, with a course of frovatriptan during the week of menstruation if needed.

Anti-CGRP Monoclonal Antibodies (mAbs)

Anti-CGRP mAbs are injectable medications with long half-lives that can be administered subcutaneously (erenumab, galcanezumab, fremanezumab) or intravenously (eptinezumab). Benefits of CGRP blockade in migraine are contingent upon the role of CGRP in cranial nociception, which was discussed in Part 1 of this series.

CGRP plays a role in a number of diverse physiological functions. CGRP is a potent vasodilator and participates in blood pressure regulation. It also affects wound and fracture healing, bone turnover, and gastrointestinal motility among other functions. CGRP-containing sensory fibers innervate blood vessels and the myocardium, regulating vascular resistance and blood flow to various organs. [91].

Postmarketing surveillance shows that erenumab can cause elevated blood pressure in people with or without pre-existing hypertension. One retrospective study of 61 identified cases of elevated blood pressure showed that 42/61 (69%) cases did not have pre-existing hypertension, and

28/61 (46%) noted an elevated blood pressure within a week after first dose of erenumab [92]. These findings eventually led to safety-related labeling changes by the FDA in April 2020 [93]. At this time, association of hypertension with other anti-CGRP mAbs has not been established.

CGRP has a protective effect on myocardium in response to ischemia. In an experimental model of myocardial ischemia in rats, CGRP mediated hemodynamic and metabolic protection with a potent vasodilatory effect on the coronary microvasculature [94]. Human studies with CGRP-blocking agents in those with cardiovascular risk factors are limited. A randomized, double-blind, placebo-controlled study evaluated the effect of intravenous erenumab on exercise time during a treadmill test in participants with stable angina and found no significant changes in exercise time compared to placebo [95].

Infusion of CGRP during the acute phase of subarachnoid hemorrhage (SAH) demonstrated a protective role of CGRP against vasospasm [96, 97]. In those at risk for aneurysm rupture, the safety of long-term CGRP antagonists is not known. Scoring systems, such as PHASES, can help assess aneurysmal rupture risk [98], although their utility when determining safety of an anti-CGRP mAb in patients with cerebral aneurysm is not known. A detrimental effect of short-acting small molecule CGRP antagonists on outcomes of cerebral ischemia was demonstrated in mice, posing the theoretical risk that ischemic stroke in the presence of long-term CGRP blockade with mAbs could be worse [99]. A case of stroke associated with the CGRP inhibitor erenumab has been reported in the literature, raising an awareness to this association, although the reported case also had confounders [100].

Cases with both new Raynaud's phenomenon (RP) and worsening of prior RP have been reported [101]. A retrospective study showed such findings with the use of anti-CGRP mAbs in about 5% ($n = 9$) of patients; however, there were confounders such as use of triptans for acute treatment in all 9 patients and beta blockers in 6 [102].

Apart from cardiovascular effects, CGRP also has anabolic effects on dynamic bone tissue via upregulation of angiogenic markers [103]. Both CGRP and its receptor play crucial roles in bone regeneration and healing of fractured bones. Bone regeneration was shown to be profoundly impaired in mice with global CGRP inactivation [104]. This raises the question whether prolonged blockade of CGRP with either mAbs or chronic use of gepants can impair healing of bone fracture or contribute to bone loss [105]. As migraine is more common in women, it is important to remember that postmenopausal women are at higher risk for osteoporosis, especially if using multiple medications that can affect bone turnover. In such patients, signs for osteoporosis should be monitored and treated accordingly. We also recommend counseling individuals with poorly healing fractures about potential risks of prolonged CGRP blockade and to wait until healing is satisfactory before initiating treatment with mAbs.

There are some gastrointestinal concerns as well. CGRP mediates the peristaltic reflex induced by mucosal stimulation or muscle stretch, leading to a known side effect of constipation with erenumab [106]. The 90-day incidence of serious constipation that results in an ER visit or inpatient admission is similar to the rate in patients with migraine treated with other commonly used migraine medications [107, 108]. A large "real world" study of erenumab showed that the rate of adverse events is significantly higher than in clinical trials, but continuation of treatment remained relatively high, and the majority of patients believed that benefits outweighed the negative effects [109, 110]. The role of CGRP in inflammatory diseases such as ulcerative colitis and Crohn's disease has been evaluated, with some animal studies demonstrating delayed ulcer healing and increased mucosal damage with CGRP blockade [111–113].

CGRP plays a role in vascular adaptation in pregnancy [91]. In humans, plasma levels of CGRP increase during pregnancy, peaking in the third trimester and returning to baseline after delivery. Levels of CGRP are lower in women with preeclampsia, a condition characterized by abnormal placentation leading to placental ischemia and eventually to maternal endothelial dysfunction [114, 115]. Given the role of CGRP in pregnancy, women that have been exposed to CGRP-blocking agents during pregnancy may be at an increased risk of hypertension and preeclampsia, although data are limited. At this time, the safety of anti-CGRP agents on the human fetus is unknown, so they should not be used in pregnancy.

Due to the vast physiological effects of CGRP, a "CGRP Antagonist Risk Scale" as suggested by Dr. L. Robbins would be a valuable clinical tool [116]. The Germany Society of Neurology and the German Migraine and Headache Society issued guidelines that advised avoidance of CGRP mAbs in patients with coronary heart disease, ischemic stroke, SAH, peripheral arterial occlusive disease, inflammatory bowel disease, COPD, pulmonary hypertension, Raynaud's syndrome, wound healing disorders, or organ transplant until further notice, and the European headache federation guideline states that more long-term studies in patients with cardiovascular comorbidities are needed to determine their safety [117, 118••].

Questions regarding anti-CGRP mAb drug interactions arise when patients are treated with biologic therapies for other conditions, for example, multiple sclerosis or rheumatoid arthritis, or when patients have concomitant use of small molecule drugs such as gepants. Biological agents such as anti-CGRP mAbs are large, complex molecules that are engineered to have high target specificity [119•]. They are catabolized to amino acids, and their metabolism does not

depend on CYP450 or drug transporters. Due to their high specificity and excretion via the reticuloendothelial system, significant risk of mAb-mAb or mAb-gepant interaction is thought to be low, although more studies regarding this are needed [119•]. Theoretical concern for excessive CGRP blockade exists among clinicians. Studies of ubrogepant in those who received therapy with erenumab or galcanezumab showed no significant changes in pharmacokinetics and no safety concerns [120]. Similarly, one small study and several single case reports found rimegepant to be safe in patients treated with erenumab, fremanezumab, and galcanezumab [121•, 122•].

Although CGRP mAbs are either fully human (erenumab) or humanized (galcanezumab, fremanezumab, eptinezumab), they still have the capacity to induce anti-drug (ADA) and neutralizing antibodies (NAbs). Several studies were conducted to address this concern and showed various rates of NAbs from 0 to 12%, with the lowest rate noted in fremanezumab and highest in eptinezumab studies [123]. ADAs and NAbs can theoretically cause loss of therapeutic effect or provoke an immune response; however, current data do not support any clinically relevant adverse events related to ADAs or NAbs against anti-CGRP mAbs. Future studies will provide further insight into the effects of long-term CGRP blockade.

Gepants

There are currently two small molecule CGRP receptor antagonists FDA-approved for the preventive treatment of migraine – rimegepant (approved on May 27, 2021) and atogepant (approved on September 28, 2021). Rimegepant and atogepant are both metabolized by CYP3A4 [124, 125]. The potential drug interactions for gepants, including atogepant and rimegepant, were reviewed in Part 1 of this series; however, one should also keep in mind the potential interaction with grapefruit and grapefruit juice. Grapefruit juice inhibits CYP3A4, which could prolong the clearance of gepants (as well as other migraine treatments metabolized through this system), so it is recommended to counsel patients to avoid regular intake of grapefruit and grapefruit juice or delay the next dose of the gepant by 48 h after consuming these foods [126–128].

CGRP inhibitors can be good acute treatment options for those with contraindications to vasoconstrictors such a triptans, but are there safety concerns with concomitant use? A small, randomized, partially blinded, placebo-controlled study of 42 participants evaluated the effects on blood pressure with coadministration of rimegepant with subcutaneous sumatriptan [129]. All participants received two subcutaneous injections of sumatriptan 6 mg on days 1 and 5 of the study. On days 2 through 5, they also received either oral rimegepant 75 mg or placebo once daily. Mean arterial pressures, diastolic blood pressures, and systolic blood pressures were measured in all participants. No significant differences in blood pressure were seen between those that received sumatriptan alone versus sumatriptan and rimegepant combined, and no clinically significant changes in pharmacokinetics were observed. Thirty-nine participants experienced one or more adverse events (most mild), with two participants noted to experience mild increases in heart rate and blood pressure. An open-label, randomized crossover study of thirty adults who received either atogepant 60 mg alone, sumatriptan 100 mg alone, or both drugs together evaluated pharmacokinetic interactions and did not find any clinically relevant effects on peak plasma concentrations or areas under the plasma concentration–time curve for either drug [130]. Study drugs were administered on days 1, 8, and 15. Four participants reported adverse events, all mild, which included somnolence after taking sumatriptan, and nausea and headache after taking atogepant along with sumatriptan. No serious adverse events occurred. To our knowledge, no studies evaluating interactions between gepants and triptans other than sumatriptan currently exist.

Clinical trials for both atogepant and rimegepant excluded patients who experienced cardiovascular events such as myocardial infarction, stroke, and transient ischemic attack within 6 months prior to enrollment [131–133]. As mentioned in Part 1, it may be prudent to avoid gepants in such patients until 6 months out from their cardiovascular event.

In patients with severe renal dysfunction or end-stage renal disease, the lowest dose of atogepant (10 mg once daily) should be used, and those undergoing dialysis should wait until after their dialysis session is complete before taking a dose [125]. No dosing adjustments for rimegepant are needed in those with mild, moderate, or severe renal impairment; however, its use in those with end-stage renal disease should be avoided due to lack of data [124]. Both rimegepant and atogepant should be avoided in those with severe hepatic impairment.

Conclusion

Treatments for migraine preventive therapy include specific and nonspecific options. Guidelines based on efficacy are available, but risks for side effects and adverse drug reactions also need to be considered (Table 1). Nonspecific migraine treatments such as anticonvulsants, beta-blockers, and some antidepressants are associated with various side effects but can also be used to treat comorbid disorders. Migraine-specific preventive medications, such as long-term CGRP blocking agents, appear to be safe in most patients. However, theoretical risks have been posited, and clinicians should be aware of emerging long-term safety concerns. More "real-world" studies are needed to determine long-term safety of CGRP blocking medications.

Table 1 Mitigation strategies for side effects of migraine prophylactic drugs

Drug class	Mechanism of action	Major contraindications and safety concerns	Potential risk mitigation strategies
Beta-blockers	Inhibit epinephrine and norepinephrine from binding to beta-adrenergic receptors CNS effects: block 5HT-2C and 5HT-2B receptors, modulate noradrenergic and GABA-mediated processes, inhibit nitric oxide synthase	Depression, disordered sleep, bronchospasm, peripheral vasoconstriction, impaired glucose metabolism, interaction with triptans	Avoid in longstanding or refractory depression, or reactive airway disease Consider hydrophilic beta blockers to avoid CNS side effects Supplement melatonin in cases of insomnia Consider nebivolol in cases of metabolic syndrome Decrease dose of rizatriptan to 5 mg when used with propranolol
AED: Valproate	CNS effects: facilitates GABAergic activity, affects CGRP activity	Parkinsonism, weight gain, hepatotoxicity, pancreatitis, teratogenic, male infertility	Limit use to less than 14 months if possible Screen for insulin resistance, hepatic and pancreatic disorders Avoid use in overweight or obese individuals Avoid use in women of childbearing age not on effective methods of contraception Avoid use in men with infertility
AED: Topiramate	CNS effects: facilitates GABAergic activity, affects CGRP activity	Cognitive impairment, anxiety, AACG, paresthesia, renal calculi, carbonation dysgeusia, interactions with contraceptives, teratogenic	Titrate dose gradually and use extended-release formulations when possible Avoid in cases of significant baseline anxiety Monitor for visual changes first 2 weeks of starting treatment Encourage adequate hydration and consumption of potassium-rich foods Avoid use in women of childbearing age not on effective contraception
Antidepressants: Amitriptyline (TCA) Venlafaxine (SNRI)	Serotonergic, noradrenergic, anticholinergic effect, antihistamine effect on H1 and H2 receptors	Hyponatremia, somnolence, dry mouth, urinary retention, constipation, weight gain, cardiac arrhythmia, orthostatic hypotension, hypertension, sexual dysfunction	Keep a low threshold for testing for signs of hyponatremia Use nighttime dosing Encourage hydration and oral hygiene Choose TCA with least anticholinergic properties Encourage physical activity and a high fiber diet. Monitor for constipation, discontinuation of therapy may be necessary in severe constipation Monitor weight. If possible, avoid usage in obese patients Screen for QT prolongation, avoid in patients with arrhythmia, avoid polypharmacy with multiple QT prolonging medications Avoid usage with prior orthostatic hypotension. Use nortriptyline over other TCAs Monitor blood pressure regularly Ask about sexual dysfunction on subsequent visits. Lower the dose or switch to alternate therapy as necessary

Table 1 (continued)

Drug class	Mechanism of action	Major contraindications and safety concerns	Potential risk mitigation strategies
Anti-CGRP monoclonal antibodies	CGRP ligand or receptor binding antibodies, antagonist effect	Constipation, hypertension, poor wound healing, impaired bone healing	Monitor for constipation. Discontinuation of therapy may be necessary in severe cases Blood pressure monitoring in patients with risk factors Age-appropriate screening and management of osteoporosis in postmenopausal women Counsel patients with moderate to high cardiovascular risk factors, inflammatory bowel disease about potential risks
Gepants	Small molecule CGRP receptor antagonists	Cardiovascular safety concerns if used during an acute cerebrovascular or cardiovascular event, concern if used in those with severe renal dysfunction, end-stage renal disease, or severe hepatic impairment, interaction with grapefruit and grapefruit juice	Avoid gepants in patients with an acute stroke or myocardial infarction for 6 months Use atogepant 10 mg in severe renal dysfunction or end-stage renal disease, and dose after dialysis Avoid rimegepant in end-stage renal disease Avoid rimegepant and atogepant in severe hepatic impairment Avoid regular consumption of grapefruit and grapefruit juice. Consider waiting 48 h after consumption before taking gepant

Compliance with Ethical Standards

Conflict of Interest Dr. Chua has received honoraria as a speaker for Allergan, Amgen, Biohaven and Eli Lilly. Dr. Mehla has no disclosures. Dr. Orlova has no disclosures.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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